*REVIEW ARTICLE*

# Functional Imaging of Intervention Effects in Stroke Motor Rehabilitation

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ABSTRACT. Hodics T, Cohen LG, Cramer SC. Functional imaging of intervention effects in stroke motor rehabilitation. Arch Phys Med Rehabil 2006;87(12 Suppl 2):S36-42.

**Objective:** To assess intervention-specific effects on cortical reorganization after stroke as shown by available functional neuroimaging studies.

**Data Sources:** We searched Medline for clinical trials that contained the terms *stroke*, *reorganization*, and *recovery*, as well as either *positron-emission tomography* and *PET*, *near-infrared spectroscopy* and *NIRS*, *single-photon emission tomography* and *SPECT*, or *functional magnetic resonance imaging* and *functional MRI*; we reviewed primary and secondary references.

**Study Selection:** Articles that reported neuroimaging findings as a result of a specific treatment involving more than 1 subject were included.

**Data Extraction:** We included clinical trials that contained the terms *stroke*, *reorganization*, and *recovery*, as well as functional neuroimaging data findings as a result of a specific treatment involving more than 1 subject.

**Data Synthesis:** Included studies differed clearly from one another with regard to patient characteristics, intervention protocol, and outcome measures. Most studies used functional magnetic resonance imaging and a motor paradigm. Studies were limited in size.

**Conclusions:** Despite the methodologic differences, several common features can be identified based on the reviewed studies. Clinical improvements occurred even late after injury, after subjects were deemed to have reached a recovery plateau. This clinical improvement was accompanied by cortical reorganization that depended on the type of intervention as well as other factors. This review also suggests direction for future research studies.

**Key Words:** Magnetic resonance imaging; functional; Motor skills disorders; Positron-emission tomography; Rehabilitation; Stroke.



DESPITE EFFORTS IN PREVENTION and acute treatment, stroke remains the leading cause of adult disability in the United States and many western countries. Most patients show some spontaneous recovery of function in the weeks and months after a new stroke.[1,2] Because neurons are not thought to regrow in large numbers within the adult human brain, this recovery likely occurs on the basis of reorganization of surviving brain elements. Despite this, most patients are left with substantial impairments, resulting in disability and reduced ability to perform activities of daily living.

A number of promising therapeutic advances are emerging in the field of stroke rehabilitation. Some of these therapies target patients during the acute phase and others during the chronic phase. Examples of restorative therapies include cell-based approaches,[3,4] selective serotonin reuptake inhibitors,[5,6] catecholaminergics,[7-9] brain stimulation,[10-14] robotic and other device-based interventions,[15,16] mental imagery–based protocols,[17] and constraint-induced movement therapy (CIMT) plus other intensive physical therapy regimens.[18-21] None of these is yet universally accepted for enhancing outcome after central nervous system injury, such as stroke, though there is mounting evidence to support the notion that higher-intensity training results in better functional outcome.[22] Most approaches are currently being studied at the preclinical or early-phase human clinical trial stage.

A better insight into biologic mechanisms underlying functional recovery and potential target for these restorative therapeutics might facilitate clinical yield. Which subset of stroke patients are most likely to derive treatment-related gains, and can they be identified by neuroimaging or neurophysiologic techniques? Can the optimal dose of therapy be defined for the individual patient by these studies? Functional neuroimaging provides insights into brain function that are relevant to these questions.[23-25] Indeed, in some conditions, functional neuroimaging provides insights into disease processes when anatomic imaging or behavioral assessments do not.[26-31]

There have been only a few studies dealing with the issue of the neural substrates underlying functional recovery facilitated by *therapeutic* interventions, although such data are likely of substantial value to maximizing effect of restorative approaches. Differentiating reorganization due to therapeutic effects from spontaneous recovery provides an initial step on the road leading to neuroimaging-guided treatments that are tailored to the patient's specific need. These studies usually compare similar groups of patients in the therapeutic and control groups, using a longitudinal design that examines cerebral activation patterns before and after intervention. An intervention that is effective in improving clinical variables may shift cortical activation, mimicking the activation pattern of the well-recovered group, or develop a specific different activation pattern.

A body of functional neuroimaging literature exists regarding brain events underlying spontaneous recovery after stroke.[23-25] In sum, better functional recovery is associated with preserved activity in primary cortices.[32-34] Lesser outcome is accompanied by emergence of adaptive mechanisms, including increased activation within secondary cortical areas[35] and the intact hemisphere, and the reduced extent to which interhemispheric balance is lateralized.[36-39] Recovery from diaschisis[40] and restitution of function in ischemically insulted, but surviving brain areas[41] might also be important to return of behavior in the early period after a stroke.

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The current review focuses on available data on the effects of restorative interventions on functional magnetic resonance imaging (fMRI)–based assessments of brain function in patients with stroke. Although examples exist of other brain mapping modalities to probe treatment effects in stroke recovery, such as positron-emission tomography (PET),[42] single-photon emission tomography (SPECT),[43] or transcranial magnetic stimulation (TMS),[21,44] fMRI has been used most often in this regard. Near-infrared spectroscopy (NIRS) was used in 2 studies[23,45] evaluating the superficial cortical changes during spontaneous recovery from stroke. fMRI as a technique provides a window into functional activity in multiple brain areas, and has good accessibility, safety, and spatial resolution. Strengths and weaknesses of available studies to date are considered and future directions are discussed.

## REVIEW OF THE LITERATURE

A Medline search was performed for clinical trials that contained the terms *stroke*, *reorganization*, and *recovery*, as well as either *positron-emission tomography* and *PET*, *near-infrared spectroscopy* and *NIRS*, *single-photon emission tomography* and *SPECT*, or *functional magnetic resonance imaging* and *functional MRI*. Primary and secondary references were then examined. Articles that reported neuroimaging findings as a result of a specific treatment involving more than 1 subject were included.

There were no studies evaluating treatment effects using NIRS. Kononen et al[43] performed a SPECT study to assess 12 chronic stroke patients at rest before and after 2 weeks of CIMT and found increased perfusion in motor-related areas. PET was used to explore training-induced plasticity as a result of CIMT in 16 patients more than 1 year after subcortical infarction,[21] and in another report, PET was used to study task-oriented motor learning that facilitates shoulder and proximal arm muscle activity.[42] The latter study included 10 subcortical stroke patients within the first 12 weeks of the index event who were unable to perform active forearm movements; therefore a passive movement paradigm was used. One PET study[46] evaluated cerebral activation changes as a result of treatment of neglect. One studied the effects of piracetam to enhance the effects of language therapy.[33] Two articles examined treatment-related language recovery[47,48] using fMRI in total of 5 subjects. Both found evidence of cortical reorganization in response to differing treatment using blood oxygenation-level dependent (BOLD) or time-to-peak[48] change as a primary outcome measure.

A total of 13 fMRI motor studies published over 4 years were identified (table 1). Each of these studies examined motor deficits and used a movement-based task during fMRI. Most of these studies were focused on upper-extremity motor recovery; however, 2 reports evaluated the lower extremity.[49,50] The majority of studies (10/13) enrolled only well-recovered patients who could perform a distal motor task at baseline.

The location and extent of stroke lesions is variable, with approximately half of the patients having subcortical strokes, one third cortical strokes, and the remainder a cortical plus subcortical or brainstem stroke. Although right- and left-hemispheric lesions are represented equally in these studies, other demographic information of research subjects is different from that of the general stroke populations. For example, twice as many male as female subjects participated in the research studies. The mean age of stroke patients in the United States is 73 years,[51-53] but the mean age of research participants in these functional imaging studies is 10 to 20 years younger. Patients whose motor deficits are accompanied by cognitive difficulties, neglect, visual field cut, or multiple prior strokes—situations that are commonplace among stroke patients—are generally excluded. Note that in all but 1 fMRI study,[5] enrollees were in the chronic phase of stroke.

Clinical factors such as medications used, as well as the presence or absence of depression, may influence the observed cerebral activation pattern; however, these variables are not reported in any of these fMRI studies (appendix 1). None of the studies reports vascular reserve, cerebral blood flow, or the incidence of large artery disease, measures of relevance to fMRI after stroke. Ideally all patients should be screened for altered cerebrovascular reserve before study participation, because perfusion defects caused by large vessel disease or even small vessel disease may interfere with the BOLD signal. Also, apart from 1 study,[54] the rate with which studies are discarded because of excessive head movement was not described.

Ten of the 13 fMRI studies used a form of physical or occupational therapy, including 5 studies evaluating CIMT. You et al[50] used an innovative virtual reality technique to enhance physical training. Electric stimulation in the form of peripheral neuromuscular stimulation[55] on the extensor muscles and brain epidural stimulation was evaluated.[31]

The primary clinical and functional imaging outcome measures, when stated, have varied significantly between studies (see table 1).

A number of different motor tasks have been used to activate the brain during fMRI. Liepert[56] and Pariente[5] and colleagues have used passive hand movements. Most investigators have used active movements, such as making a fist,[57] wrist extension,[31,58] arm flexion and extension,[59] finger flexion and extension,[5,54,60] finger tapping,[31] sequential finger tapping with opposition,[57,61] tracking a sinus wave with the finger[55,62] or foot,[49] and knee flexion and extension.[50] Feedback guiding movement has been either auditory[5,50,54,57-59] or visual.[49,55,60,62]

The rate and range of movement used to activate brain motor systems has also varied across studies and has included 0.25,[31] 0.33,[59] 0.4,[49] 0.5,[50] and 1Hz,[5] as well as "maximum"[57,60] and "comfortable"[61] rates. Range of motion was specified in a minority of studies.[5,49,50,59]

Task performance was monitored by goniometer,[49,55] potentiometer,[62] camera,[50,59,60] visually in the scanner,[5,54] and by electromyography before scanning.[54,59]

There was substantial variability in acquisition methods, including scanner strength, field of view, and choice of imaging parameters such as time to repetition and echo time.

## DISCUSSION OF LITERATURE FINDINGS

The studies reviewed have a number of features in common. However, differences are apparent that provide insights into the utility of functional imaging, in particular, fMRI for understanding treatment effects after stroke. The current review also identifies several areas that require further study.

This review found the most data on the functional anatomy of motor recovery. Motor deficits represent a major component of poststroke disability, being present in more than half of all chronic stroke patients.[1,63] Performance of these studies is facilitated because motor tasks are well integrated in the neuroimaging environment and provide a measurable controllable behavioral outcome. Reports evaluating the effects of intention and attention treatments in aphasia (n=2)[47,48] are not discussed in table 1 because of methodologic differences with studies of motor function.

Most published studies have focused on patients with good to excellent outcomes at baseline because they were more able to perform the motor tasks required for neuroimaging measurements. Additionally, rigorous entry criteria for therapeutic investigations and pragmatic difficulties with scanning contrib-

**Table 1: Studies Using fMRI to Study Effects of Restorative Poststroke Therapy**

| Study | Treatment N (M/F) | Mean Age (y)* | Handedness (R/L) | Side of Lesion (R/L) | Control Group | Hours Rehab Therapy | Type of Rehab Therapy | Time From Stroke Onset* | Lesion Location | Primary Clinical Outcome Measure | Primary fMRI Outcome Measure |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lindberg et al[58] | 10 (8/2) | 56.4 | 2/0 | 2/0 | None | 10–13 | Active-passive movement training | 25.3 | 2 cortical | MCP joint extension, UE MAS | Voxel count, voxel intensity |
| Kimberley et al[55] | 16 (11/5) | 60.1±14.5 | 14/2 | 8/8 | Sham-treated stroke patients† | 60 | Extensor NMES | 35.5 | 3 cortical,10 subcortical, 1 cortical & subcortical, 2 brainstem | Box and block, MAL, JTHT | Voxel count, voxel intensity, Intensity Index |
| Luft et al[59] | 21 (12/9) | BATRAC, 63.3±15.3 DMTE, 59.6±10.5 | NR | 14/7 | DMTE-treated stroke patients | 6 | BATRAC, DMTE | 50.3 | 12 cortical, 6 subcortical, 3 brainstem | UE FMA, WMFT | Voxel count |
| Pariente et al[5] | 8 (5/3) | 61.7 | NR | 3/5 | Placebo-treated stroke patients | Single session | Fluoxetine vs placebo | 0.5 | 7 subcortical, 1 brainstem | Finger tapping | Voxel intensity |
| Schaechter et al[54] | 4 (3/1) | 57±17 | 4/0 | 1/3 | Healthy subjects | 40 | CIMT | 12.5 | 2 cortical, 1 subcortical, 1 brainstem | MAL, UE FMA, WMFT | Laterality Index, voxel count, voxel intensity |
| Carey et al[62] | 10 (6/4) | 65.7±13.3 | 9/1 | 4/6 | Healthy controls‡ and stroke patients† | 13.5–20 | Finger tracking | 56.4 | 1 cortical, 6 subcortical, 2 cortical & subcortical, 1 brainstem | Box and block, finger tracking | Voxel count, Laterality Index |
| Johansen-Berg et al[68] | 7 (5/2) | 55.6 | 6/1 | 3/4 | None | 14 | CIMT | 37.6 | 6 cortical, 1 subcortical | Grip strength, UE Motricity Index, JTHT | Laterality Index, voxel count, *z* score, recovery-weighted activation |
| You et al[50] | 10 (7/3) | 54 | NR | 7/3 | Stroke patients | 20 | Virtual reality | 19.3 | 10 subcortical | FAC, mMAS | Laterality Index, voxel count |
| Levy et al[61] | 2 (1/1) | 48.5 | 1/1 | 1/1 | None | 30 | CIMT | 6.8 | 2 cortical | WMFT, MAL | Laterality Index, voxel count |
| Kim et al[57] | 5 (5/0)§ | 54.8 | 5/0 | 2/3 | None | 98 | CIMT | 21.4 | 4 cortical | FMA, 9-hole peg test, JTHT | Voxel count |
| Liepert et al[56] | 15 | NR | NR | NR | None | 60 | CIMT | NR | NR | MAL | NR |
| Cramer et al[31] | 12 (6/6) | 61 | 9/2+1 ambidextrous | 4/8 | None | 45 | OT ± epidural stimulation | 23 | 2 cortical, 6 subcortical, 3 cortical & subcortical, 1 brainstem | UE FMA | Activation volume, location voxel of maximum activation |
| Carey et al[49] | 1 (1/0) | 50 | 1/0 | 0/1 | None | 12 | Tracking exercises | 20 | 1 brainstem | Ankle movement measures | Voxel count, voxel intensity, Intensity Index |
| Total | 121 (66%/34%) | 58 | 86%/12% | 50/49 | | 32 | | 26 | 34 cortical, 47 subcortical, 6 cortical & subcortical, 10 brainstem | | |

Abbreviations: BATRAC, bilateral arm training with auditory cueing; DMTE, dose-matched therapeutic exercise; F, female; FAC, Functional Ambulation Category; FMA, Fugl-Meyer Assessment; Intensity Index, (intensity task minus intensity rest)/intensity rest; JTHT, Jebsen-Taylor Hand Test; L, left; M, male; MAL, Motor Activity Log; MCP, metacarpophalangeal; mMAS, modified Motor Assessment Scale; NMES, neuromuscular electric stimulation; NR, not reported; OT, occupational therapy; R, right; UE, upper extremity; WMFT, Wolf Motor Function Test arm test.

*Total treatment group, in months, mean values except median for Luft et al.[59]

†Control patients crossed over to treatment.

‡Five treatment, 4 controls.

§Includes 1 trauma patient.

uted to this bias in patient selection. As a consequence, less is known about the functional anatomy of therapy-induced recovery processes in patients with more severe deficits after stroke. This issue is problematic because patients with poor recovery represent the largest fraction of the target population, and for those persons there is virtually no available treatment. A clear limitation of the available literature is that missing information on clinical and perfusion-related data reduces the ability to generalize results from these studies to the general population of stroke patients.

Functional neuroimaging tasks can be performed in block design, when long epochs of repetitive activity are interleaved with rest periods; or in event-related design, where single movements alternate with long rest periods. All published functional neuroimaging studies that evaluated the effect of an intervention on brain plasticity used a block design. It should be kept in mind that an event-related design might contribute additional information. This technique models the hemodynamic changes and offers the potential to minimize fatigue by using isolated simple behaviors to activate the brain.[64] Additionally, an event-related design might contribute to reduced confounds generated by analysis of erroneous or poorly performed trials. However, event-related design has its limitations, such as reduced signal.

Imaging results vary across studies, influenced by many factors including patient characteristics, treatment content, and pharmacologic regimen. Among the subset of studies examining effects of CIMT on fMRI activation during movement of the affected hand,[56,57,60,61] the main finding was generally a treatment-associated increase in activation within the ipsilesional primary motor cortex, dorsal premotor cortex, and supplementary motor area.[57,60] Consistent with this finding, a regimen of intensive finger tracking training resulted in clinical improvements that were accompanied by a change in laterality index from negative to positive,[62] a finding that reflects relatively greater involvement in or contribution from components of the motor network in the ipsilesional hemisphere. Studies using virtual reality[50] or fluoxetine[5] also emphasized a treatment-related shift toward increased ipsilesional activation. These treatment-related ipsilesional increases are concordant with findings in PET[21,65] and most,[44,66] but not all,[67] TMS studies. One study[54] after CIMT showed increment in bilateral activation. Most study results support the view that performance improvements found after this particular therapy strategy are associated with a reconfiguration of the motor network that is similar to that identified in healthy age-matched controls.[21] Some of these changes are reminiscent of those evidenced in the process of skill acquisition in healthy humans.

After a different form of interventional therapy, bilateral arm training,[59] involving patients with more severe deficits, more prominent activity was found in *contralesional* motor areas, suggesting that baseline clinical deficits or interventional therapies influence how treatment modifies fMRI results. Similarly, Schaechter et al[54] provided CIMT to patients who were weaker than those enrolled by Johansen-Berg et al,[68] and the former group found more contralesional activation increase with therapy, whereas the latter group found more ipsilesional activity with therapy. It must also be noted that bilateral arm training with auditory cueing therapy emphasizes bilateral movements that involve proximal limb, the latter known to be more bilaterally organized than distal limb.[69] The finding of contralesional changes with this intervention, therefore, might also suggest that treatment content might also influence fMRI results.

The study by Pariente et al,[5] in which the serotonergic drug fluoxetine was associated with changes in fMRI findings, as well as the altered PET findings using piracetam,[33] also underlines the potentially important influence of medications in stroke recovery trials, both on baseline blood flow and as a function of performance of a motor task.

Another important difference between studies is the time interval between stroke onset and functional neuroimaging. Spontaneous motor recovery after stroke is generally considered to be complete by the end of the third month postinfarct.[1,63] All but one of the studies listed in table 1 enrolled patients well beyond this point. Intensive exercise programs were effective in producing plastic changes and motor improvement even at a delayed time frame in several of these studies, where the mean time from onset was 26 months (see table 1). However, the functional neuroimaging correlates of treatment gains in subjects with chronic stroke, who are no longer showing spontaneous behavioral recovery, might be very different when compared with findings in subjects in the active phase of spontaneous stroke recovery. This consideration requires further study.

Physical therapy during epidural cortical stimulation was associated with reduced activation within ipsilesional motor cortical areas.[31,70] This reduction might be an effect of stimulation, and might correspond to effects of motor learning in some models,[71] events seen during spontaneous stroke recovery,[35] remote effects of stimulation,[72] or thalamic plasticity.[73] A recent study[74] pointed to the usefulness of a range of forms of cortical stimulation.

## CONCLUSIONS

Functional neuroimaging at present provides an effective tool to evaluate mechanisms underlying functional recovery after stroke. Studies are needed to better understand the effects of various interventions according to lesion site, recovery level, sex, and age. Additionally, methodologic advances are likely to improve in the future; for example, electromyographic and kinematic tools to monitor motor activity during scanning, crucial for an accurate interpretation of neuroimaging data. Understanding drug effects at baseline and on task-related fMRI activation will allow more extensive use of this tool in the neurorehabilitation setting. It is possible that when this information becomes available, clinical gains derived from restorative interventions will be maximized if guided by imaging results. Results from functional neuroimaging theoretically have unique value for understanding biologic effects of therapeutic interventions, to predict treatment responses and triage, and to tailor dose according to brain state rather than clinical examination.

This review identified 88 patients in whom fMRI was performed and several patients studied using PET (n=26) or SPECT (n=12) in parallel with a poststroke motor restorative intervention. Although there are many differences in patient characteristics, intervention, and neuroimaging study design, certain common features emerge. Improved motor behavior, accompanied by reorganization of cortical function, occurs even months or years after a patient has reached the plateau that defined spontaneous recovery after stroke.[63,75] Increased reliance on original, contralateral control mechanisms is associated with behavioral gains, as has been suggested in brain mapping studies of spontaneous recovery,[23-25] though this may be less true in more severely affected patients and those undergoing bilateral training.

This review suggests a number of needed future research directions. Further studies are needed to examine functional imaging correlates of treatment effects within nonmotor domains, such as language and neglect. Measures of injury,[76-79] physiology,[80,81] and clinical predictive models might be combined with functional imaging measures to best address the

goal of optimizing restorative therapy. Study of a broader fraction of the stroke population is needed. Vascular pathology can influence fMRI results.[82-86] Studies using fMRI to evaluate treatment effects in stroke patients therefore would have increased impact if measures of arterial status and cerebral perfusion were included. In addition, nearly all functional neuroimaging of restorative interventions after stroke have relied on fMRI. Use of alternate methods is to be promoted, in part to address reliability of fMRI results and to examine fMRI validity in stroke patients.

Noninvasive neuroimaging techniques allow the study of the working human brain and suggest that functionally important adaptation occurs after focal injury. A higher degree of understanding of the underlying neurobiologic principles that drive these changes will make it possible to design targeted interventions to minimize impairment in stroke patients.

## APPENDIX 1: PATIENT-RELATED FACTORS THAT CAN INFLUENCE FMRI RESULTS

- Prestroke disability, experience, and education
- Age
- Hemispheric dominance
- Stroke topography including volume and location
- Clinical deficit and disability from stroke
- Acute stroke therapies
- Time after stroke
- Medications
- Medical comorbidities, eg, hypertension or diabetes mellitus
- Psychiatric comorbidities, eg, depression
- Type and amount of rehabilitative therapies
- Arterial pathology, eg, stenosis or vascular reserve capacity
- Ascertainment bias, eg, those related to MRI contraindications (claustrophobia or pacemaker)

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